REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

As noted in the Office Action Summary, claims 1, 7, 11-15, 19 and 25-40 are pending. Claims 1, 7, 11-15, 19, and 25-32 are canceled herein without prejudice or disclaimer thereto. Applicants reserve the right to file at least one continuation or divisional application directed to any subject matter canceled by way of the present Amendment.

Claim 33 is amended herein to address an issue of grammar. New claims 41-57 are added. Support for these new claims may be found throughout the specification and claims as-filed, especially at page 14, lines 16-18 and claim 12 (support for claims 41 and 46); page 14, lines 16-18 and claim 13 (support for claims 42 and 47); page 4, lines 19-22 and claim 33 (support for claims 43-44 and 48-49); page 24, lines 24-25 and claim 33 (support for claim 45); claim 34 (support for claim 50); claim 35 (support for claim 51); claim 36 (support for claim 52); claim 37 (support for claim 53); claim 38 (support for claims 54 and 57); claim 39 (support for claim 55); and claim 40 (support for claim 56). Thus, no new matter is presented by way of the present Amendment.

Objection to claim 33

Claim 33 stands objected to for the recitation of " MIP-1αor". This typographical error has been addressed by amending claim 33 to recite "MIP-1α or". Applicants request that this objection be withdrawn.

Rejections Under 35 U.S.C. § 112, first paragraph

Claims 33-40 stand rejected under 35 U.S.C. § 112, first paragraph, as purportedly failing to comply with the written description requirement. Specifically, the Office asserts that claims 33-40, as previously added, introduce new subject matter into the application, as the specification as-filed purportedly fails to disclose "wherein the IL-2 and MIP chemokine work together synergistically to inhibit the growth or cause the rejection of a tumor in said patient when compared to the anti-tumor response in said patient administered with a composition comprising a vector comprising only the nucleic acid sequence (i) or the nucleic acid sequence (ii)" as recited in claim 33. The inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q. 2d 1111, 1117 (Fed. Cir. 1991). To this end, the subject matter of the claim need not be described literally (*i.e.*, using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement. *See* M.P.E.P. § 2163.02. Applicants submit that in light of the specification, it would be clear to the skilled artisan that Applicants had possession of the subject matter of claims 33-40 in the application as of the filing date.

Lines 17-20 of page 3 recite "We have now identified novel cytotoxic compositions in which the various constituents are chosen so as to obtain a synergistic effect of their respective activities and improved properties of said constituents" [underlined emphasis added]. However, the Office argues that the specification does not describe "a synergistic effect". Applicants disagree.

With regard to the synergistic effect, Applicants note that the term "synergistic" is used in the common, ordinary definition of the word, in that it refers to the cooperative action of separate molecules providing a greater effect together than if taken independently. In support of this assertion, Applicants refer to the present specification. Page 3, lines 17-20, referred to above, support this definition or "synergistic" by reciting "to synergistic effect of their respective activities" and "improved properties of said constituents". Here, "synergistic", refers to the greater cytotoxic (anti-tumor) effect provided by combination of the two constituents, compared to the lesser effect of taking each constituent taken alone.

The Office asserts that it is unclear as to how the compositions of the invention show anti-tumor protection, if tumors are already present on the animal. By way of clarification, Applicants note that the term "protection" is intended to mean "providing benefit", in that the compositions of the invention provide anti-tumor protection. The compounds of the present invention provide protection from the harmful effects of tumors, as they are able to increase the life-span of the subject or delaying tumor development. However, to avoid confusion Applicants refer to "anti-tumor activity" instead of "anti-tumor protection".

With regard to the support for claims 33-40 as provided by the figures of the application, Applicants submit the following. The Office states that Figure 2 does not display a synergistic combination using MIP-1alpha and IL-2 because the survival rate for IL-2 is longer than MIP-1alpha and IL-2 combined. Applicants note that the experiment such as that shown in Figure 2 would be considered by the skilled artisan in its general context, and that there may be some divergence between individual animals. For example, there may be spontaneous regression in some individual

subjects, as is likely with one mouse included in the group treated with IL-2. However, a small deviation observed in one individual out of an entire group does not preclude the general conclusion shown by the mean. Applicants refer to the 50% survival rate, as well as that 50% of the mice treated with acid nucleic sequences encoding only MIP-1 alpha exhibit a 14-day survival. 50% of the mice treated with acid nucleic sequences encoding IL-2 exhibited a 22-day survival, whereas 50% of the mice treated with acid nucleic sequences encoding both MIP-1 alpha and IL-2 exhibited a 32-day survival. Therefore, when considering the mean survival rate, the skilled artisan would conclude that treatment of tumors with nucleic acid sequences encoding both MIP-1 alpha and IL-2 is more effective than treatment with MIP-1 or IL-2 alone, because the combination therapy provides a higher survival rate.

The Office states that Figure 4 and 5 fail to provide support, and argues that that IL-2 and MIP-1 alpha + IL-2 have a similar decrease in tumor burden. However, Applicants point out that Figures 4-5 compare the tumor volume and survival rate measured in animals treated with the combination of MIP-1 beta + IL-2, compared to either IL-2 or MIP-1 beta. As with Figure 3, tumor development is clearly inhibited in mice treated with nucleic acid sequences encoding both IL-2 and MIP-1 beta (resulting in 500 mm^3 volume in average at day 27 with a stabilization of tumor burden). In contrast, mice treated with nucleic acid sequences encoding IL-2 alone show a continuous tumor development throughout the experiment duration with tumor volume reaching 1000mm^3 at day 27. The slope of tumor progression is dramatically increased in mice treated with nucleic acid sequences encoding MIP-1 beta alone (tumor volume of 4100 mm^3 on average at day 27).

The measurement of survival rate illustrated in Figure 4 is the same. Fifty percent (50%) of the mice treated with acid nucleic sequences encoding only MIP-1 beta exhibited a 27-day survival and 50% of the mice treated with acid nucleic sequences encoding IL-2 exhibit a 43-day survival. Yet 50% of the mice treated with acid nucleic sequences encoding both MIP-1 beta and IL-2 exhibit 52 day survival. Moreover, 37% of mice survived for more than 100 days after being treated with IL-2 and MIP-1 beta in combination. The proportion of surviving mice is greatly reduced following treatment with IL-2 alone, and non-existant following treatment with MIP-1 beta alone (all the mice died within a period of 41 days). Therefore, these figures are clearly exhibiting a synergistic effect, as the mice receiving both components had a markedly greater life-span compared to mice who received only one component.

The synergistic effect provided by the combination of a MIP chemokine + IL-2 is also apparent from Figures 5 and 6. In this experiment, the anti-tumor activity of the combination of MIP-1 alpha + IL-2 was compared to the activity caused by combinations involving either IL-2 or MIP-1 alpha and another molecule known for having anti-tumor properties, namely IFNg. As shown in Figure 5, tumor development was stabilized in mice treated with nucleic acid sequences encoding both IL-2 and MIP-1 alpha while continuous tumor development is observed in mice treated with nucleic acid sequences encoding IL-2 and IFNg and a rapid progression of tumor growth is seen in mice treated with nucleic acid sequences encoding MIP-1 alpha and IFNg. The survival rates shown in Figure 6 confirm the improved efficacy of the combination MIP + IL-2, as compared to other combinations, and thus support and provide basis for the synergistic effect of the present invention. Sixty seven percent of mice treated with the composition of the invention survived for more than

90 days post injection, while 50% of the mice treated with acid nucleic sequences encoding IL-2 and IFNg exhibited a 21-day survival (with a 22% rate of tumor regression) and 50% of the mice treated with acid nucleic sequences encoding both MIP-1 alpha and IFNg exhibited a 27-day survival (no tumor regression).

Thus, these results demonstrate that IL-2 and a MIP chemokine work in cooperation to provide a more effective anti-tumor activity than if taken alone. The administration of nucleic acid sequences encoding both MIP and IL-2 to an animal increases the survival of an animal having pre-existing tumors, delays the growth of the tumors, and causes tumor regression in a significant proportion of the treated animals compared to administration of nucleic acid sequences encoding either IL-2 or a MIP chemokine. Thus, Applicants submit believe that the MIP chemokine and IL-2 work together synergistically to inhibit the growth or cause the rejection of a tumor in the patient, when compared to the anti-tumor response in said patient administered with a composition comprising a vector comprising only the nucleic acid sequence encoding a MIP chemokine or the nucleic acid sequence encoding IL-2.

The Office further asserts that the specification does not specifically point out what cytotoxic composition is able to produce the synergistic effect. Applicants note that the specification throughout states that the present invention is directed to a composition comprising a mixture of two distinct constituents that together provide a cytotoxic effect (*e.g.*, an anti-tumor activity). For example, on page 6, lines 13-23, the specification notes that the first constituent is required to be a nucleic acid encoding and expressing a MIP chemokine and the second constituent is a nucleic acid encoding and expressing a polypeptide having a cytotoxic activity, including IL-2 (*see* page 6, line 21).

Applicants further note that in response to the restriction requirement in the present case, Applicants elected claims directed to a composition comprising a vector or a mixture of vectors comprising (i) a nucleic acid sequence encoding and expressing a MIP chemokine and (ii) a nucleic acid sequence encoding and expressing IL-2. What is disclosed in the specification may be claimed, covering the full scope of elected subject matter (*e.g.*, the association of nucleic acid sequences encoding and expressing MIP chemokine and a polypeptide having a cytotoxic activity). Thus, Applicants are entitled to more specific subject matter included in the entire scope of the elected subject matter, including subject matter directed to the association of nucleic acid sequences encoding and expressing MIP chemokine and IL-2.

Applicants submit that the specification (especially the examples of the application) provide sufficient evidence that a composition encoding both IL-2 and MIP elicits a synergistic effect, and thus is more effective for increasing survival rate or inhibiting tumor development, as compared to a composition encoding either MIP or IL-2. Therefore, the elements of claims 33-40 reciting the synergistic effect provided by the MIP chemokine and the IL-2 constituents is supported by the originally filed application. Applicants request that the rejection pursuant to 35 U.S.C. § 112, first paragraph be withdrawn.

Claims Rejection Under 35 U.S.C. § 103

Claims 1, 7, 11-15, 19, 26, and 31 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Boursnell et al. (U.S. Patent No. 6,287,557) taken with Hobart et al. (U.S. Patent No. 5,147,055) and LaFace (U.S. Patent No. 6,649,158)

and Song et al., (*J. Exp. Med.,* 186:1247-1256, 1997). Claims 1, 11, 13, 15, and 25-30 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Boursnell et al. (U.S. Patent No. 6,287,557) taken with Hobart et al. (U.S. Patent No. 5,147,055) and LaFace (U.S. Patent No. 6,649,158) and Song et al., (*J. Exp. Med.*, 186:1247-1256, 1997) in further view of Bruder et al. (U.S. Patent No. 6,440,944). Claims 14, 15, 31, and 32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Boursnell et al. (U.S. Patent No. 6,287,557) taken with Hobart et al. (U.S. Patent No. 5,147,055) and LaFace (U.S. Patent No. 6,649,158) and Song et al. (*J. Exp. Med.*, 186:1247-1256, 1997) in further view of Gruber (U.S. Patent No. 6,410,326). In the interest of expediting prosecution, and without acquiescing in the rejections, claims 1-32 are deleted herein. Thus, these rejections are moot.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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